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High-Density Lipoproteins and Inflammation in Patients on Renal Replacement Therapies

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Abstract *Background/aim:* High-density lipoprotein (HDL) protects against atherosclerotic plaque formation. The present study examined the relationship between HDL serum concentrations and markers of inflammation in patients on renal replacement therapies. *Methods*: We studied 96 dialyzed patients, 62 males and 34 females, on mean age 62.1 ± 14.27 years old and 24 healthy controls. The treatment modalities which were applied were: regular hemodialysis (HD, n = 34), predilution hemodiafiltration (HDF, n = 42) and peritoneal dialysis (PD, n = 20). Dialysis adequacy was defined by Kt/V for urea and serum bicarbonate levels were measured in gas machine. Cholesterol, triglycerides, HDL and LDL concentrations were biochemically measured. Oxidized LDL (ox-LDL) and hsCRP serum concentrations were measured by ELISA. Beta2-microglobulin (beta2M) and leptin serum concentrations were measured by radioimmunoassays. *Results*: The patients presented increased beta2M, hsCRP, leptin and triglycerides than control group, but HDL exhibited significant reduction ($p < 0.05$). The patients on PD had significantly higher serum bicarbonate levels and lower oxLDL than other groups of patient ($p < 0.05$). HDL positively associated with Kt/V, presented negative correlation with both, ox-LDL and beta2M ($r = -0.237$, $p = 0.02$ and $r = -0.291$, $p = 0.004$ respectively). Beta2M was positively associated with hsCRP ($r = 0.257$, $p = 0.01$). Serum bicarbonate levels were inversely associated with hsCRP and oxLDL ($r = -0.232$, $p = 0.05$ and $r = -0.289$, $p = 0.01$ respectively). *Conclusions*: The low HDL was associated with increased beta2M concentrations in patients on renal replacement therapies. The HDL reduction was combined with an elevation of oxLDL, which was lower in PD patients compared to hemodialysis modalities patients. The acidosis state influenced both, the inflammatory environment and the increase of oxidized lipids. Dialysis adequacy was positively correlated to HDL serum concentrations.

Keywords: *hemodialysis, HDL lipoprotein, beta2-microglobulin, inflammation, hsCRP, acidosis*

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1. Introduction

End-stage renal disease (ESRD) results in atherogenic diathesis, which is mainly associated with oxidative stress, inflammation, hypertension and dyslipidemia [1,2]. Oxidative stress and inflammation promote atherosclerosis via: (1) oxidation of low-density lipoproteins (LDL), (2) activation, adhesion, infiltration and differentiation of monocytes into foam cells in the artery wall and (3) impairment of high-density lipoprotein (HDL)-mediated reverse cholesterol transport by lowering apolipoprotein AI (apo AI) and lecithin-cholesterol acyltransferase (LCAT) [3,4].

HDL protects against atherosclerotic plaque formation by mediating reverse cholesterol transport and by antioxidant, anti-inflammatory and antithrombotic actions [5,6].

In patients with ESRD plasma apo AI, the principal apolipoprotein of HDL, is significantly reduced. Also, the antioxidant and anti-inflammatory activities of HDL are impaired [1,7,8].

The effect of renal replacement therapy on HDL inflammatory properties is unkown. The present study designed to examine the relationship between HDL serum concentrations and markers of inflammation in patients on permanent renal replacement therapies.

2. Methods

2.1. Patients

We studied 96 dialyzed patients at Nephrology Department of General Hospital "Laiko" and Renal Unit of Institute "Health" in Athens. 62 males and 34 females participated in this study, on mean age 62.1 ± 14.27 years old. Patients with acute illness, significant infection or malignancy were excluded from our study.

The treatment modalities which were applied were: regular hemodialysis (HD, n = 34), on-line-predilution hemodiafiltration (on-l HDF, n = 42) and peritoneal

dialysis (PD, n= 20). The median time on hemodialysis was 5.0 ± interquartile range 3-10 years and the mean time on peritoneal dialysis was 2.8 ± 1.61 years.

The hemodialysis treatment was performed 3-times weekly with a dialysis time of 3.5-4 h per session, a filter of 1.5-2 m^2 surface area and a blood flow of 350-400 ml/min. A bicarbonate-based ultrapure buffer dialysis solution was used with a dialysate flow rate of 500-600 ml/min, a calcium concentration of 1.50-1.75 mmol/L, a sodium concentration of 138-145 mmol/L and low molecular weight heparin as anticoagulant therapy.

We used exclusively high-flux synthetic membrane, defined by a ultrafiltration coefficient > 20 ml/h [9]. Dialysis dose defined by Kt/V for urea, which was calculated according to the formula of Daugirdas [10].

All patients on peritoneal dialysis were following continuous ambulatory peritoneal dialysis (CAPD) with 4 changes per day using a combination of 2 changes of 2 L of hypertonic glucose-based solution (3.86% glucose; Baxter Healthcare) and 2 changes of 2 L of semi-hypertonic glucose solution (2.5% glucose; Ariti; Bieffe Medital S.p.A.).

20 hemodialyzed patients and 15 peritoneal dialyzed patients excreted up to 100 ml of urine per day. No patients were receiving any hypolipidemic medicine.

The underline renal disease were hypertensive nephrosclerosis (n = 31), chronic glomerulonephritis (n = 28), polycystic kidney disease (n = 12), diabetic nephropathy (n = 11), and other/unknown (n = 14).

2.2. Control Group

Twenty-four healthy subjects (12 women and 12 men, aged 56.08 ± 12.34 years) served as controls. Individuals with acute or chronic infection, acute intercurrent illnesses, hypertension, diabetes, malignancy, psychiatric disorders, or those requiring medications were excluded.

2.3. Approval and Consent

The study was approved by the ethics committee of the Hospitals "Laiko, University General Hospital of Athens" and "Renal Unit of the Diagnostic and Therapeutic Center of Athens Hygeia SA". Written informed consent was obtained from all subjects.

2.4. Blood Ccollection

Blood samples were obtained by venipuncture in the peritoneal dialyzed patients and control group in a twelve hours fasting state. In hemodialyzed patients blood was drawn just before the start of the mean weekly dialysis session also in a twelve hours fasting state from the vascular access. In the end of the treatment the blood pump speed was reduced to < 80ml/min and blood samples was obtained at 2 min post-dialysis from the arterial dialysis tubing for the calculation of the adequacy of dialysis by kt/V for urea. Samples were centrifuged immediately, serum was separated and processed for various assays.

2.5. Laboratory Measurements

Albumin, cholesterol, triglycerides, high density lipoproteins (HDL) and low density lipoproteins (LDL) were measured by biochemical analysis and hematocrit level was also checked. Serum bicarbonate levels were measured in gas machine.

The concentrations of beta2-microglobulin (beta2M) and leptin serum concentrations were measured by radioimmunoassays (Immunotech by Beckman, Czech Republic and Active Human Leptin IRMA DSL-23100i, Webster, USA).

High sensitivity C-reactive protein (hsCRP) and oxidized LDL (ox-LDL) levels were measured using enzyme linked immunoabsorbed assays (ELISA, Immundiagnostik AG., Germany and Immundiagnostik AG. Stubenwald-Allee, Bensheim respectively) according to manufacturer's specifications.

Normalized protein catabolic rate for dry body mass (nPCR) was calculated from the urea generation rate [11]. Body mass index (BMI) was obtained from height and post-dialysis body weight.

2.6. Data Analysis

Data were analyzed using SPSS 15.0 statistical package for Windows (SPSS Inc, Chicago, Illinois) and expressed as mean ± standard deviation or as median value ± interquartile range for data that showed skewed distributions; differences between mean values were assessed by using one-way ANOVA analysis and paired-t test. Correlations between variables were defined by Spearman coefficient and p values less than. 05 were considered significant and x^2 analysis was used for the correlation between categorical variables. We built a linear regression analysis to examine the relationship of HDL serum concentrations with variables.

Table 1. Characteristics of the studied population, n = 96 [Haemodialysis, HD, n = 76, Peritoneal dialysis, PD, n = 20 (62 males / 34 females)]

Characteristic	*minimum*	*maximum*	*Mean / median*	*SD / interquart range*
Age (years)	24	87	62.10/	14.27/
Haemodialysis duration (years)	0.5	27	/5.0	/3 - 10
Peritoneal dial duration (years)	1	6	2,8/	1.61/
Body mass index (Kg/m2)	18.10	43.50	25.08/	3.86/
Kt/V for urea (n = 96)	1.20	2.52	/1.35	/1.26 – 1.72
Normalized protein catabolic rate (nPCR, g/Kg/day) (n = 96)	0.97	3.41	2.23/	0.616/
Urine volume (ml/day)	100	1500	337.35/	305.8/
Serum bicarbonate levels(mmol/L)	14.8	25.8	20.64/	2.59/
beta2-microglobulin (mg/L)	8.29	138.0	/25.98	/16.1 – 32.7
Leptin (ng/ml)	0.28	36.6	9.52/	8.9/
hsCRP (mg/L)	0.12	21.35	8.65/	5.9/
ox-LDL (ng/ml)	29.9	867.09	/60.63	/48.8 – 96.6
cholesterol (mg/dl)	90.0	398.0	163.4/	45.35/
Triglycerides (mg/dl)	49.0	445.0	172.15/	87.12/
HDL (mg/dl)	17.0	69.0	38.89/	9.69/
LDL (mg/dl)	27.6	310.2	90.49/	37.18/
Albumin (gr/dl)	1.4	4.6	3.88/	0.44/
Htc (%)	23.9	45.3	35.5/	4.13/

3. Results

Characteristics of the studied population at the time of inclusion are listed in Table 1.

Compared with the control group, the dialyzed patients exhibited marked elevation of serum beta2M, hsCRP, leptin and triglycerides concentrations ($p < 0.05$).

Serum HDL cholesterol concentrations exhibited significant reduction in patients compared to control group ($p < 0.05$, Figure 1).

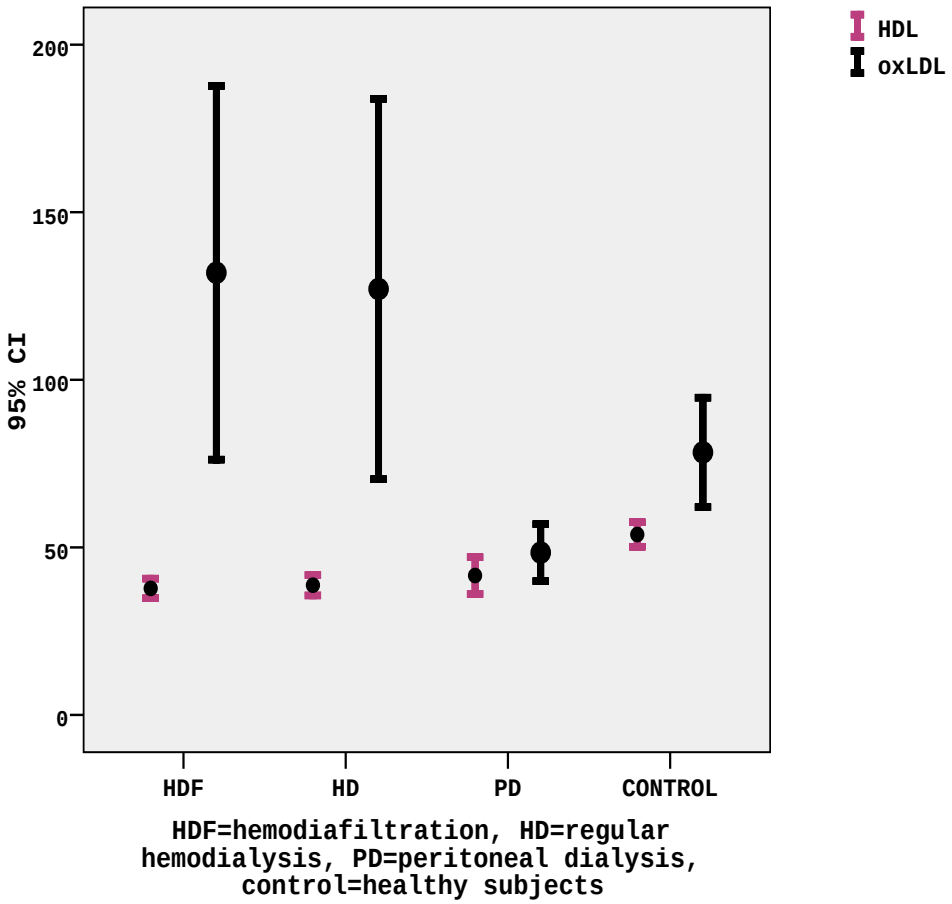


Figure 1. HDL and oxidized LDL (oxLDL) serum concentrations in hemodiafiltration, regular hemodialysis, peritoneal dialysis groups of patients comparatively to healthy subjects

Table 2. Linear regression analysis for the relationship between HDL and beta2-microglobulin serum concentrations after adjustment for traditional and specific factors in patients on renal replacement therapies (n = 96)

	Standardized Beta B	Sig.	95% confidence interval for B Lower Bound	Upper Bound
Beta2-microglobulin	-0.271	**0.013**	-0.159	-0.019
age	0.151	0.18	-0.046	0.241
Diabetes mellitus	-0.059	0.59	-7.95	4.57
Hypertension	0.037	0.73	-3.39	4.79
Smoking	-0.028	0.80	-5.57	4.34
Treatment duration	-0.038	0.76	-0.461	0.338
Dialysis modality	-0.011	0.94	-4.23	3.96
BMI	-0.091	0.42	-0.76	0.32
Kt/V for urea	0.174	0.23	-2.89	11.74

Serum beta2M concentrations were inversely associated with HDL serum concentrations ($r = -0.291$, $p = 0.004$) and positively with hsCRP concentrations ($r = 0.257$, $p = 0.01$). Supportingly, linear regression analysis confirmed the negative impact of beta2M concentrations on HDL levels after adjustment for traditional and specific factors in this population of patients [B = -0.271, Cl95% (-0.159 to -0.019), p = 0.013, Table 2]. Also, the patients with high beta2M values (higher than the median value = 26 mg/L) simultaneously had low HDL concentrations (lower than the mean value = 38.8 mg/dl) ($x^2 = 9.379$, $p = 0.004$, Figure 2).

On the other hand, we observed significantly positive correlation between hsCRP and leptin concentrations ($r = 0.341$, $p = 0.002$, Figure 3). Also, serum bicarbonate levels were inversely associated with hsCRP and oxLDL concentrations ($r = -0.232$, $p = 0.05$ and $r = -0.289$, $p = 0.01$ respectively).

HDL serum concentrations presented negative correlation with ox-LDL serum concentrations ($r = -0.237$,

p = 0.02), although the relationship between HDL and Kt/V was significantly positive (r = 0.206, p = 0.04).

We examined the patients on hemodialysis separately from the patients on peritoneal dialysis. We observed that the patients on hemodialysis presented significantly Dependent Variable: HDL reverse correlation between beta2M and HDL concentrations and between serum bicarbonate levels and hsCRP (r = -0.338, p = 0.003 and r = -0.384, p = 0.005 respectively).

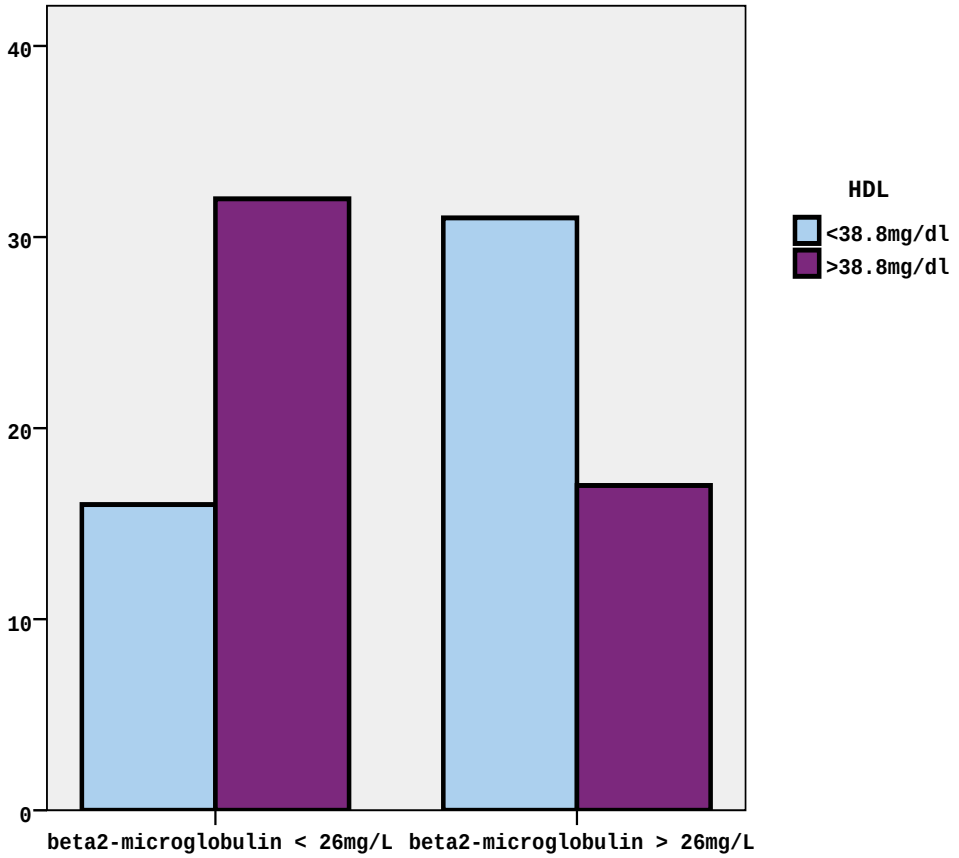


Figure 2. HDL serum concentrations in patients with values of beta2-microglobulin serum concentrations higher or lower than the median value = 26 mg/L

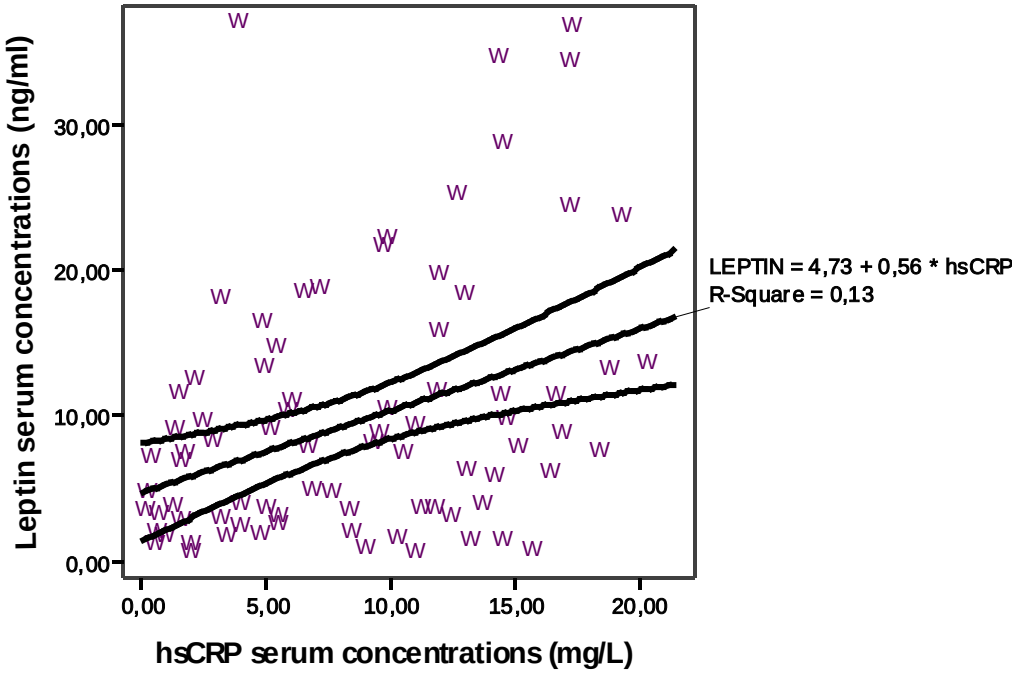


Figure 3. Positive correlation between hsCRP and leptin serum concentrations in studied patients (n = 96, p = 0.002)

In peritoneal dialysis patients beta2M concentrations were positively associated with leptin and hsCRP levels (r = 0.542, p = 0.02 and r = 0.698, p = 0.001 respectively) and inversely with serum bicarbonate levels (r = -0.451, p

= 0.04). Also, hsCRP and leptin levels were positively associated (r = 0.564, p = 0.01).

Examining the control group separately we observed that the relationship between hsCRP, beta2M and leptin concentrations was found significantly positive (r = 0.660, p = 0.001 and r = 0.696, p = 0.001 respectively) similarly to peritoneal dialysis group of patients.

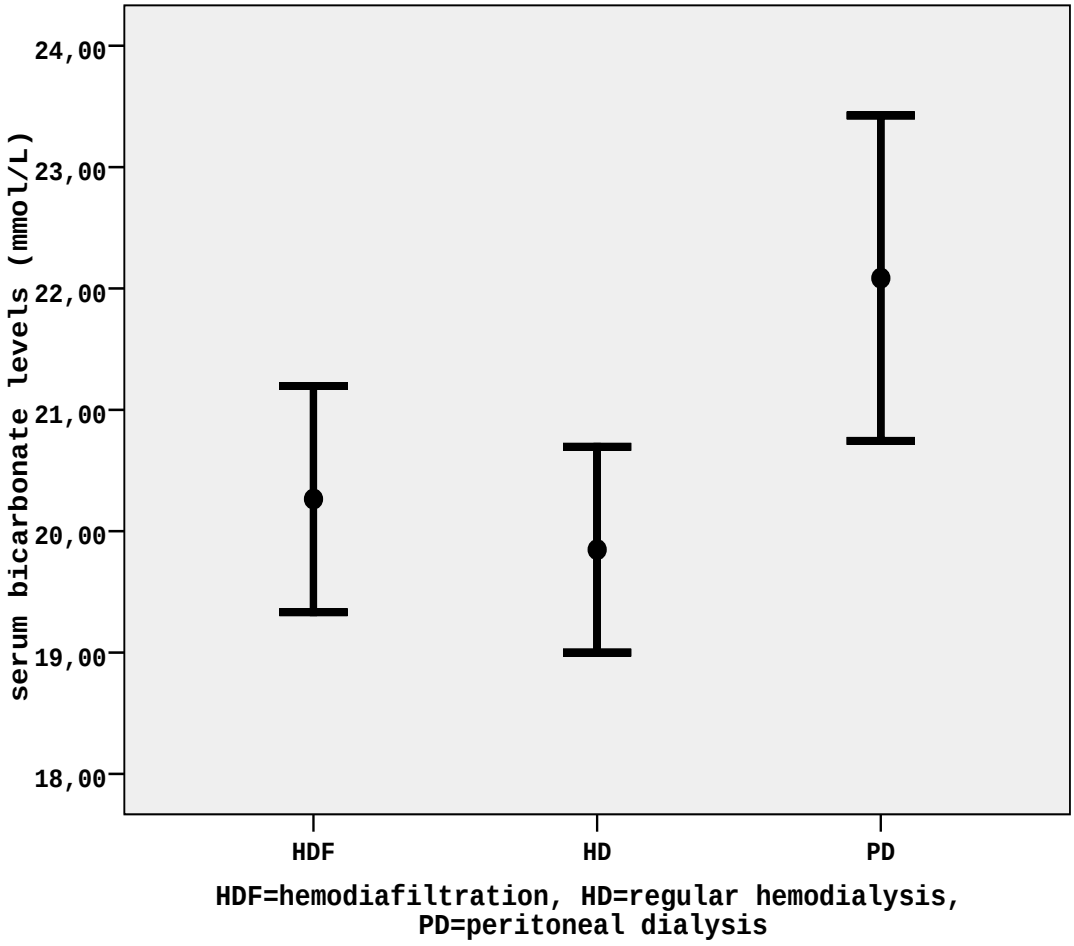


Figure 4. Serum bicarbonate levels in patients on hemodiafiltration, regular hemodialysis and peritoneal dialysis

Comparing the patients according to dialysis modality between them, we observed that the patients on peritoneal dialysis presented significantly higher serum bicarbonate levels and lower ox-LDL serum concentrations than the patients on hemodialysis ($p < 0.05$, Figure 1 and Figure 4). Also, they presented significantly higher BMI and Kt/V for urea, although nPCR was significantly lower than in patients on hemodialysis ($p < 0.05$). hsCRP, leptin and LDL concentrations were higher in peritoneal dialysis patients despite without statistically significant difference, but beta2M, HDL and triglycerides serum concentrations were similar in every group of patients.

4. Discussion

Chronic renal failure leads to profound dysregulation of HDL and triglyceride-rich lipoprotein metabolism, resulting in HDL deficiency and hypertriglyceridemia [1].

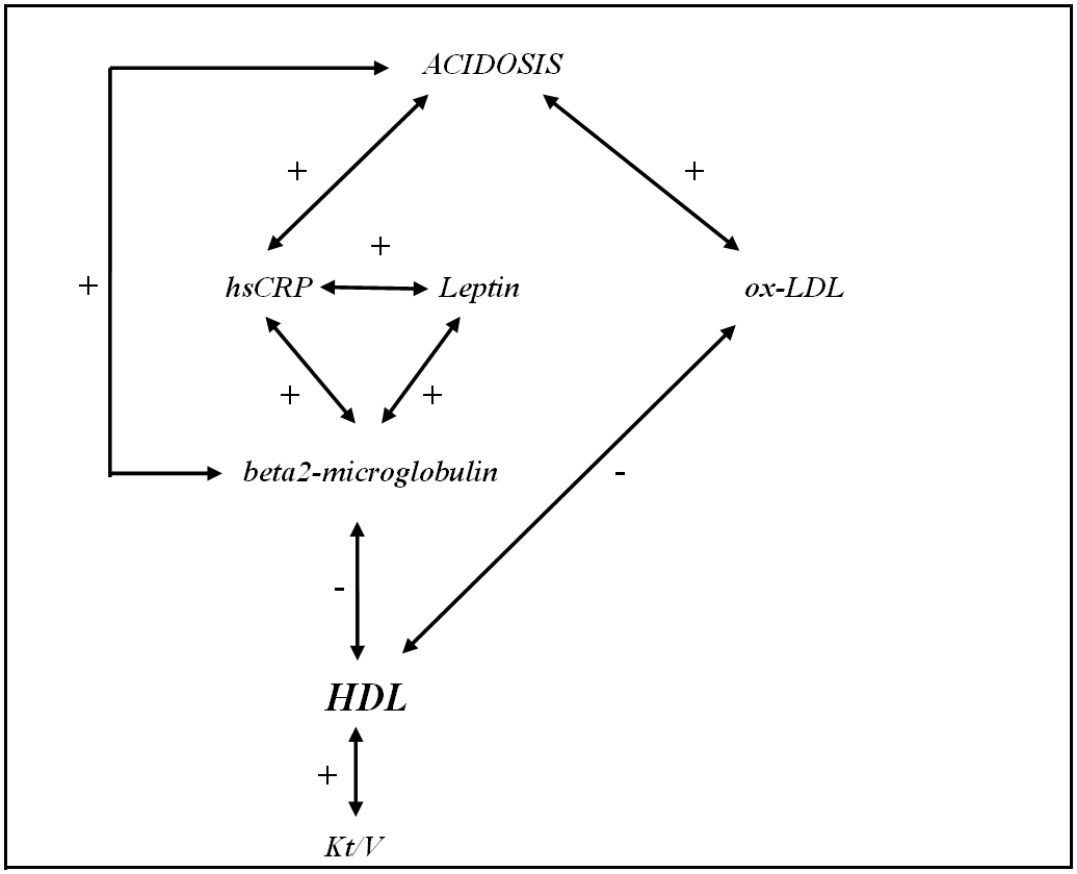
Hypertriglyceridemia in patients with advanced chronic kidney disease is associated with increased concentration of plasma very low-density lipoproteins (VLDL) and chylomicron. These abnormalities due largely to downregulations of lipoprotein lipase, hepatic triglyceride lipase, and LDL receptor-related protein, VLDL receptor, reductions of apo E concentrations and apo CII to apo CIII ratio in combination to impaired clearance of lipoproteins [12,13,14]. Additionally, HDL cholesterol concentration and its maturation are reduced, although HDL triglyceride content and pre-β HDL are elevated in this population [15]. These disorders due mainly to reduction of apo AI, apo AII and LCAT [16].

In this study, HDL serum concentrations were found reduced although triglycerides concentrations elevated in patients compared to control group.

On the other hand, ESRD patients exhibit marked oxidative modification of lipids and lipoproteins. Lipoprotein oxidation is a common condition in this population of patients, associated to uremic environment and metabolic acidosis, another usual conditions in these patients [17]. Additionally, it has been already reported that acidosis promotes inflammation releasing cytokines [18]. Indeed, in this study, we observed significant impact of metabolic acidosis on both, elevated oxidized LDL levels and hsCRP serum concentrations in total patients and separately in patients on hemodialysis modalities (Picture 1).

In the present study, HDL serum concentrations were inversely associated with both, ox-LDL serum concentrations and beta2M serum concentrations in total patients and examining separately the patients on

hemodialysis modalities (Picture 1). The influence of beta2M serum concentrations on HDL levels was also significant after adjustment for traditional factors and specific for these patients factors, as dialysis modality, dialysis duration, BMI, Kt/V for urea. In addition, the patients with higher beta2M values presented simultaneously lower HDL values.



Picture 1. Observations of present study: Associations between HDL serum concentrations, acidosis, oxidation, inflammation and beta2-microglobulin serum concentrations in patients on permanent renal replacement therapies

It has been reported that beta2M has an important role on immunity and inflammation and its association with atherosclerosis could be explained by vascular inflammation [19,20]. In agreement, in this study serum beta2M concentrations were positively associated with hsCRP serum concentrations, which, in the meantime, presented significant correlation with leptin serum concentrations. Leptin is an adipocyte, that is produced by adipose tissue and may modify the systemic inflammatory response. Leptin high levels were correlated with proinflammatory activity, in accordance to our findings [21]. Supportingly, we also observed significantly positive correlation directly between leptin and beta2M serum concentrations in peritoneal dialysis group of patients, who presented higher leptin levels compared to hemodialysis group of patients, despite without statistically significant difference. However, there are controversial findings for the relationship between elevated concentrations of leptin and chronic inflammation and it has been suggested that leptin may be a negative acute phase protein in chronic hemodialysis patients [22].

In support to the inflammatory activity of leptin, in this study we observed a significant relationship between hsCRP serum concentrations and both, the leptin and beta2M serum concentrations in healthy subjects, similarly as for with the dialyzed patients, despite the fact that the mean values of these molecules were significantly higher in patients than in healthy subjects.

Neverthless, the reduction of HDL concentrations in ESRD patients is compounded by severe reduction of HDL anti-oxidant activity and heightened pro-inflammatory properties of LDL [7,23]. These events contribute to the atherogenic diathesis in these patients. Also, it has been showed that systemic inflammation reduces anti-oxidant and anti-inflammatory activity of HDL, known as *acute-phase HDL* [24]. The reduction of anti-oxidant/anti-inflammatory properties of HDL in dialysis patients must be due, at least in part, to the inflammatory environment as evidenced by significant elevation of IL-6 in their plasma. This may support the finding of this study for the inverse relationship between HDL and beta2M serum concentrations, despite we did not examine the activity of HDL in the present study.

Moreover, in this study we observed significantly positive association between acidosis level and beta2M serum concentrations separately in peritoneal dialysis group of patients (Picture 1). Preliminary evidence suggested that metabolic acidosis may play a role in the accumulation of beta2M seen in dialyzed patients [25]. However, we did not find a such significant association between serum beta2M levels and serum bicarbonate levels in total patients or separately in hemodialysis modalities groups of patients. In peritoneal dialysis group of patients we also found significantly higher serum

bicarbonate levels in combination with lower ox-LDL levels comparatively to hemodialysis modalities groups of patients. It is known that peritoneal dialysis has as an advantage the holding of a better acidosis level than hemodialysis modalities and this may have as a result the severely lower ox-LDL concentrations in peritoneal dialysis patients.

The effect of hemodialysis on the LDL inflammatory and HDL anti-inflammatory properties is unclear. By removing potentially pro-oxidant and proinflammatory uremic toxins, dialysis may attenuate LDL inflammatory activity and restore HDL anti-inflammatory properties. Indeed, in this study we observed significantly positive correlation between HDL serum concentrations and Kt/V for urea, which is an indicator of the dialysis adequacy (Picture 1).

The mechanism by which hemodialysis reduces inflammatory activity of LDL and improves anti-inflammatory activity of HDL in ESRD patients is presently unknown. Previously, it has been shown that the conversion of HDL to a proinflammatory agent seen in the predialysis plasma samples obtained from the ESRD patients was associated with significant reduction of paraoxonase 1 and glutathione peroxidase activities. Paraoxonase 1 is a major HDL-associated antioxidant enzyme, which can prevent formation of proinflammatory oxidized lipids and lipoproteins such as oxidized LDL [25]. Partial restoration of paraoxonase activity in the postdialysis plasma samples could have contributed to the anti-inflammatory HDL activity, mainly if hemodialysis can be determined as severely adequate by the current Kt/V for urea. This may be an explanation for the inverse relationship between HDL and ox-LDL serum concentrations in combination with the positive correlation of HDL with Kt/V for urea in this study.

However, hemodialysis procedure attenuates, but does not fully reverse these abnormalities. Additionally, blood exposure to dialysis membrane, mechanical stress in the pump and influx of impurities from dialysate compartment during dialysis procedure can acutely intensify the inflammatory state and LDL and HDL inflammatory activities.

On the other hand, the heparin used during dialysis may play an important role on LDL and HDL properties, as in addition to its anticoagulant and antithrombotic properties, heparin has a significant lipolytic activity due to its ability to cause rapid release into the circulation of lipoprotein lipase and hepatic lipase [26]. Similarly, heparin administration can raise plasma antioxidant capacity [27]. This is in part due to the ability of heparin to cause the release of extracellular superoxide dismutase [28]. The rapid release of lipoprotein lipase and hepatic lipase in the circulation can promote hydrolysis of triglycerides and phospholipids contained in the circulating lipoproteins, increasing the removal of their fatty acid contents. Since the inflammatory activity of ox LDL is in part mediated by their oxidized fatty acid and phospholipid contents, it could be assumed that the improvement in LDL and HDL inflammatory activity observed after hemodialysis can be a result of the systemic heparinization during dialysis procedure.

Neverthless, in this study oxLDL serum concentrations were lower in peritoneal dialysis patients in whom were not using systematically heparin, than in patients on hemodialysis modalities in whom were using systemic heparinization during every dialysis session. But, in peritoneal dialysis patients together with the lower ox-LDL coexisted a better acidosis level, which should be the cause for the reduced concentrations of oxidized lipids comparatively to the hemodialysis modalities patients, rather than the heparin use.

The findings of this study (Picture 1) could suggest that the correction of acidosis state results in lower levels of oxidized lipids and in an impaired inflammatory environment in dialyzed patients. On the other hand, the improvement of dialysis treatment adequacy contributing to a reduction of beta2-microglobulin, as an inflammation and acidosis associated indicator, may have as an effect the elevation of HDL serum concentrations that could prove beneficial for patients undergoing renal replacement therapies.

5. Conclusions

The low HDL serum concentrations were associated with increased beta2-microglobulin serum concentrations, as a factor of vascular inflammation, in patients on permanent renal replacement therapy. The HDL reduction was combined with elevation of oxidized LDL serum concentrations, which were lower in peritoneal dialysis patients comparatively to the patients on hemodialysis modalities. The acidosis state influenced both, the inflammatory environment and the abnormalities of oxidized lipids. Dialysis adequacy was positively correlated to HDL serum concentrations.

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